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Acute Coronary Syndromes

ERK5 IS A NOVEL REGULATOR OF PLATELET ACTIVATION AND CONTRIBUTES TO INFARCT EXPANSION AND CARDIAC DYSFUNCTION AFTER MYOCARDIAL INFARCTION

Poster Contributions
Hall C
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Background: Mechanisms which cause dysregulated platelet function during MI are under-estimated and poorly understood. Extracellular regulated protein kinase 5 (ERK5), a mitogen known to protect endothelial and myocardial cells, is present in platelets but appears to promote platelet activation.

Methods: Human platelets were stimulated with agonists including ADP, U46619, TRAP and convulxin, or reactive oxygen species (ROS; hypoxia, hydrogen peroxide, sodium cyanide). ERK5 activity was detected using a phospho-specific antibody. Platelet activation was assessed via FACS for P-selectin or activated GPIIb/IIIa. Arteriole thrombus formation was assessed by intravital microscopy during FeCl3 injury. MI was performed in WT mice +/- aspirin and in platelet specific ERK5-/- mice by LAD coronary artery ligation. Left ventricular (LV) function was determined by echocardiography.

Results: Human and mouse platelet ERK5 is phosphorylated in response to thrombin and thromboxane receptor stimulation, but not purinergic or collagen receptor stimulation. Human platelets with ERK5 inhibitor pre-treatment or mouse platelets with genetic ERK5 deletion had markedly blunted activation to only thromboxane or thrombin receptor agonists. Hypoxia and ROS increase WT platelet activation, but not ERK5-/- platelet activation. Thrombus formation in vivo is attenuated in ERK5-/- mice. Surprisingly, mice with focal LAD ischemia showed marked platelet dysregulation, global systolic dysfunction, with larger infarcts compared to ERK5-/- mice or WT mice treated with aspirin.

Conclusions: ERK5 mediates specific receptor-dependent platelet activation and receptor-independent activation by ROS. Dysregulated platelet activity is accentuated by myocardial ischemia, and appears to contribute to post-MI infarct expansion and cardiomyopathy in an ERK5-dependent manner. Platelet ERK5 may be a hitherto undiscovered redox sensor contributing to infarct expansion after an acute MI. This study provides insight into understanding dysregulated platelet function and suggests a new therapeutic target for treating acute MI.